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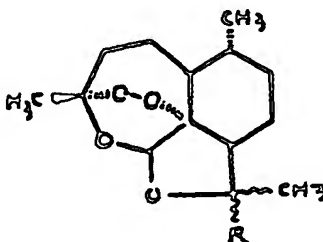
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54 9-Substituted compounds of 3 alpha, 11 alpha-Epoxy-3,4,5, 5a alpha,6,7,8,8a,9,11,11a-undecahydro-3
beta, 6 alpha, 9-trimethylfurano[3,4-][1,2]-benzodioxepin, processes for their preparation and their
use as antiprotozoal and antiviral agents.

57 Compounds of formula I

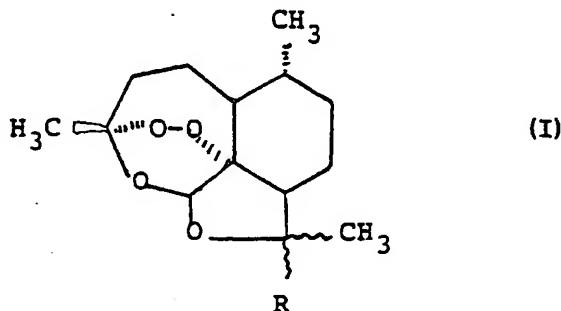


in which the substituted R has the given meaning, have an antimalarial and an antiviral activity.

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The invention relates to novel 9-substituted compounds of 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-3 β ,6 α , 9-trimethylfurano[3,4-j][1,2]benzodioxepin, pharmaceutically acceptable salts thereof and processes for their preparation and their use against protozoal and viral infections.

9-Substituted 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin compounds of the invention are represented by the general formula I



wherein R stands for

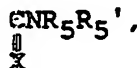
CHO;

COR₁,

wherein R₁ stands for hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl group;

CH₂OR₂,

wherein R₂ stands for hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, dialkylamino alkyl group or 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α , 9,10,12 β ,12 α -dodecahydro-3 β ,6 α ,9 β -trimethylpyrano[4,3-j][1,2]-benzodioxepin-10-yl or a group COR₃, wherein R₃ stands for alkyl, substituted alkyl group, or a group SO₂R₄, wherein R₄ stands for alkyl or aryl group, or a group



wherein

X denotes O or S,

R₅ stands for hydrogen,

R₅' stands for alkyl or aryl group or

NR₅R₅', stands for heterocycle;

COR₆R₇,

wherein R₆ stands for hydrogen, alkyl, R₇ stands for hydrogen, alkyl, aryl, alkyl group or R₆ and R₇ together with the nitrogen to which they are attached form a heterocycle which may contain an additional hetero atom and is optionally substituted at one or more places;

CH = CR₈R₉,

wherein R₈ stands for hydrogen, carboxyalkyl and R₉ stands for carboxyalkyl, aryl or heterocycle;

COSR₁₀,

wherein R₁₀ stands for alkyl, substituted alkyl or aryl groups; and pharmaceutically acceptable salts thereof.

In the formulae presented herein the various substituents are illustrated as joined to furano (3,4-j)(1,2)-benzodioxepin nucleus by one or two notations, a solid line (—) indicating a substituent in which is in the β -orientation (i.e. above the plane of the molecule) and a broken line (---) indicating a substituent which is in the α -orientation (i.e. below the plane of the molecule). The formulae have all been drawn to show the compounds in their absolute configuration. In as much as the starting materials having furano-(3,4-j)(1,2)-benzodioxepin nucleus are derived from naturally occurring materials, they as well as the final products have a furano(3,4-j)(1,2)benzodioxepin nucleus in the single absolute configuration depicted herein. The processes of the present invention, however, are intended to apply as well to the synthesis of furano(3,4-j)-(1,2)benzodioxepines of the racemic series.

In addition to the optical centers of furano(3,4-j)(1,2)-benzodioxepin nucleus, the substituents thereon

may also contain chiral centers contributing to the optical properties of the compounds of the present invention and providing a means for the resolution thereof by conventional methods, for example, by the use of optically active acids. A wavy line (-) indicates that substituents can either be in the α -orientation or β -orientation. The present invention comprehends all optical isomers and racemic forms of the compounds of the present invention where such compounds have chiral centers in addition to those of the furano(3,4-j)-
 5 (1,2) benzodioxepin nucleus.

The term alkyl stands for C₁-C₈ straight or branched chain carbon compounds such as methyl, ethyl, propyl, butyl, isopropyl, t-butyl. The term alkenyl stands for straight or branched chain carbon compounds containing one or more double bonds. Suitable examples are acryl, stearyl, cinnamyl.

10 The term alkynyl stands for straight or branched chain carbon compounds containing one or more triple bonds and may in addition contain a double bond. Examples of alkynyl groups are 3-methyl-1-pentynyl, 1-butylnyl, 3-methyl-1-butylnyl, 2-butylnyl-1-hydroxymethyl.

Substituents of substituted alkyl, alkenyl and alkynyl are halogen, hydroxy, carboxy, nitrile, acyl, aryl, heterocycle or a group NR₆R₇, wherein R₆ and R₇ are as defined above.

15 The term aryl stands for a phenyl group which is optionally substituted by one or more substituents such as halogen, alkyl, nitro, amino, hydroxy, alkoxy, carboxy, alkylcarboxylate, trifluoromethyl, substituted amino, acetyl, alkenyloxy, alkynyloxy. The term heterocycle stands for a cyclic group containing one or more hetero atoms such as piperazino, morpholino, piperidino, pyrrolidino, phthalimido, optionally substituted at one or more places by alkyl, alkoxy, hydroxy, halogen or aryl groups.

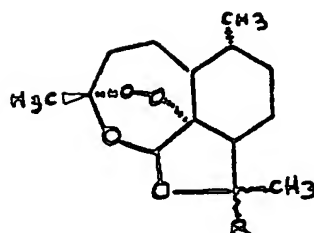
20 Preferred compounds of the invention are listed in Table 1.

Further preferred compounds of the invention are those of formula I, wherein R stands for a group CHO or CH₂OR₂, wherein R₂ has the same meaning as defined above.

Particularly preferred compounds of the invention are

- 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-formyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-
 25 benzodioxepin,
 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(2-propynyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j]-
 [1,2]-benzodioxepin,
 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(2-propenyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j]-
 [1,2]-benzodioxepin,
 30 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(p-toluenesulfonyloxy)methyl-3 β ,6 α ,9-
 trimethylfurano-[3,4-j][1,2]benzodioxepin,
 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(4-chlorophenylaminothiocarbonyloxy)methyl-
 3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin,
 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(4-fluorophenylaminothiocarbonyloxy)methyl-
 35 3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin,
 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-10 α -[3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -
 undecahydro-3 β , 6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]oxy-3 β ,6 α ,9 β -trimethylpyrano-
 [4,3-j][1,2]benzodioxepin and
 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-10 β -[3 α ,11 α -epoxy-
 40 3,4,5,5 α ,6,7,8,8 α ,9,10,11,11 α -undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]-
 oxy-3 β ,6 α ,9 β -trimethylpyrano[4,3-j][1,2]benzodioxepin.

Table 1







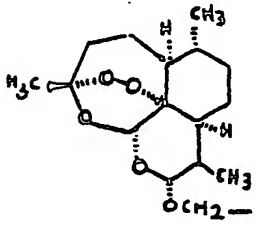
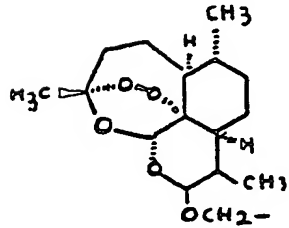
| R | M.P. °C | % Yield |
|---|---------|---------|
| CHO | 100 | 85 |
| CH ₂ OH | 135-136 | 72 |
| COOH | 166-167 | 76 |
| CH ₂ OCH ₂ CH ₂ N(C ₂ H ₅) ₂ | Oil | 47 |
| CH ₂ OCH ₂ C≡CH | 105 | 71 |
| CH ₂ OCH ₂ CH=CH ₂ | Oil | 45 |
| CH ₂ OCH ₂ CH=CH-  | Oil | 43 |
| CH ₂ OC(=O)CH ₂ Cl | Oil | 42 |
| CH ₂ OC(=O)(CH ₂) ₃ Cl | Oil | 36 |
| CH ₂ OSO ₂ -  -CH ₃ | Oil | 33 |
| CH ₂ OSO ₂ -  | Oil | 27 |
| CH ₂ OSO ₂ CH ₃ | 123 | 42 |
| CH ₂ OC(=O)NH-  -Cl | 160 | 42 |

Table 1 (cont.)

| | R | M.P. °C | % Yield |
|----|---|---------|---------|
| 5 | | | |
| 10 | $\text{CH}_2\text{OCNH}-\text{C}_6\text{H}_4-\text{Cl}$ | 89-90 | 42 |
| 15 | $\text{CH}_2\text{OCNH}-\text{C}_6\text{H}_4-\text{F}$ | 79-80 | 37 |
| 20 | $\text{CH}_2\text{OCNHCH}_2\text{CH}=\text{CH}_2$ | Oil | 23 |
| 25 | $\text{CH}_2\text{OCN}-\text{C}_6\text{H}_4-\text{N}(\text{C}_6\text{H}_4-\text{CF}_3)_2$ | 69-71 | 22 |
| 30 | $\text{CON}(\text{C}_4\text{H}_8\text{O})$ | Oil | 43 |
| 35 | $\text{CON}(\text{C}_4\text{H}_8\text{NCH}_3)$ | 93 | 43 |
| 40 | $\text{CONHCH}_2-\text{C}_6\text{H}_4-\text{CF}_3$ | 170-172 | 25 |
| 45 | $\text{COOCH}_2\text{CH}_2\text{Cl}$ | 112 | 46 |
| | $\text{COOCH}_2\text{CH}=\text{CH}_2$ | Oil | 38 |
| 50 | $\text{CH}=\text{CH}-\text{COOC}_2\text{H}_5$ (cis) | Oil | 54 |
| | $\text{CH}=\text{C}(\text{COOC}_2\text{H}_5)_2$ | Oil | 22 |
| 55 | | | |

Table 1 (cont.)

| | R | M.P. °C | % Yield |
|----|---|---------|---------|
| 5 | $\text{CH}=\text{CH}-\text{C}_6\text{H}_4-\text{CF}_3$ (cis) | Oil | 27 |
| 10 | $\text{COS}-\text{C}_6\text{H}_5$ | Oil | 26 |
| 15 | $\text{COOCH}_2\text{CH}_2\text{Br}$ | Oil | 47 |
| | $\text{COOCH}_2\text{CH}_2\text{CH}_2\text{Cl}$ | Oil | 24 |
| 20 | $\text{COOCH}_2(\text{CH}_2)_6\text{CH}_2\text{Cl}$ | Oil | 21 |
| | $\text{COOCH}_2\text{CH}_3$ | Oil | 29 |
| 25 | | | |
| 30 |  | 100 | 21 |
| 35 | | | |
| 40 | | | |
| 45 |  | 154-156 | 34 |
| 50 | ----- | | |
| 55 | | | |

| | R | M.P. °C | % Yield |
|----|-----------------------|---------|---------|
| 5 | | 150-152 | 72 |
| | CH ₂ OCOH | 84 | 55 |
| | CH ₂ OCOOH | 98- 99 | 36 |
| 10 | | 158-159 | 64 |
| 15 | | 81- 82 | 44 |
| 20 | | oil | 27 |
| 25 | | | |

The process for the preparation of compounds of the invention comprises the reaction sequence outlined in the scheme 1 wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ have the same meaning as described above.

30 The process comprises treatment of compounds of the formula II [prepared as reported in J. Med. Chem. 1989, 32, 1249-1252] with a brominating agent, preferably with liquid bromine using halogenated hydrocarbon as solvent such as carbon tetrachloride and preferably stirred for a period of one hour, then quenching with water and isolating the product of formula III from the organic layer as described herein.

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Scheme 1

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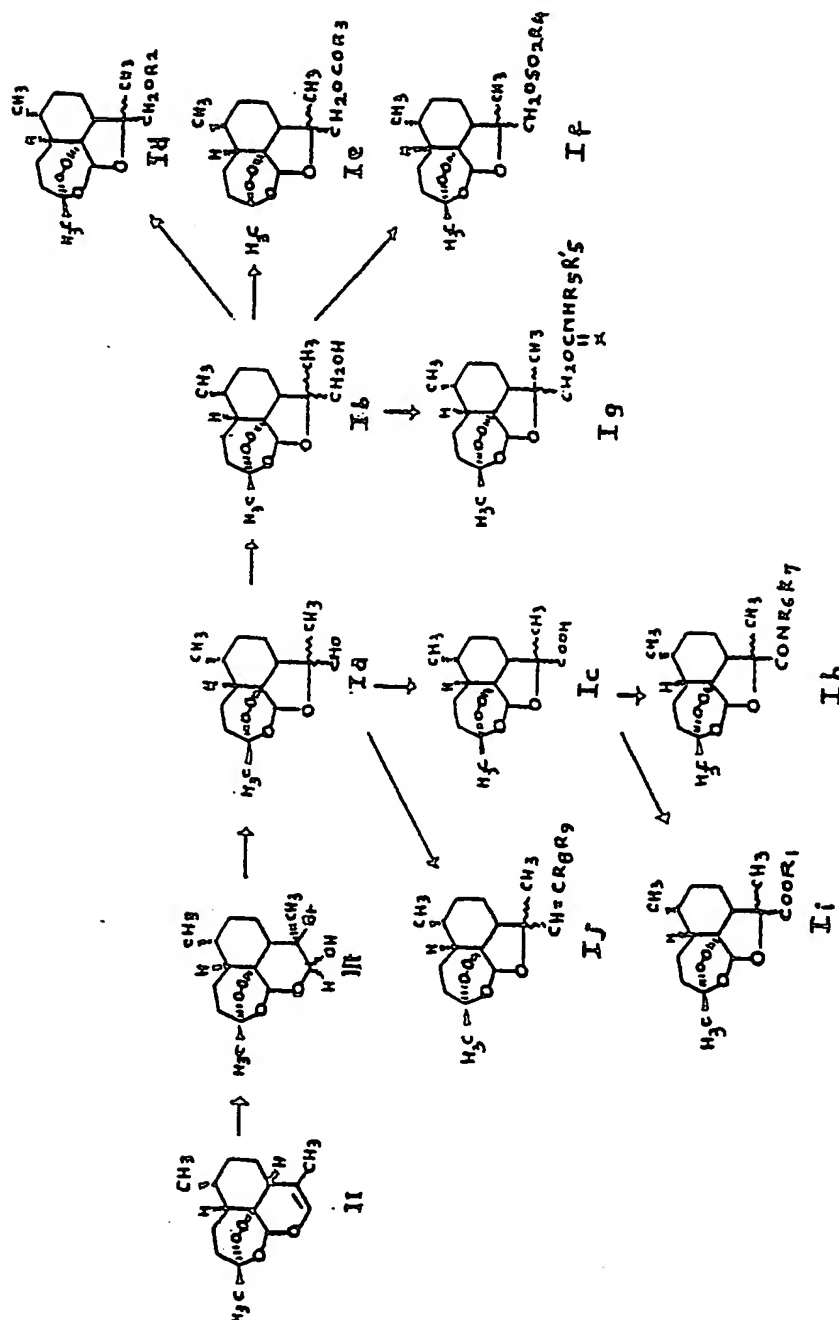
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The preparation of compounds of the formula Ia comprises treating compounds of formula III with an organic base preferably such as triethylamine, diethylamine, benzylamine or diazabicycloundecene preferably with diazabicycloundecene using organic solvent such as halogenated hydrocarbons such as chloroform, methylene chloride, carbon tetrachloride at temperatures ranging from 0 to 37°C, preferably at 27-30°C for a period of 15 minutes to 60 minutes preferably for forty to forty five minutes. Reaction mixture is

then worked up by concentration under vacuum and the residue obtained is purified by chromatography on adsorbent such as silica gel and using eluent such as chloroform to obtain compounds of the formula Ia.

Compound of the formula 1b is prepared from compound of formula Ia by treatment with reducing agents preferably such as sodium borohydride using alcohols such as ethanol, methanol, isopropanol as solvents, preferred being ethanol at temperatures ranging from 0 to 30°C preferably at 27-30°C for a period of 15 minutes to 60 minutes preferably for thirty minutes. After the completion of reaction mixture is treated with aqueous solution of ammonium chloride and then concentrated under vacuum to remove ethanol. Residue is extracted with organic solvents such as ethylacetate, chloroform, dichloromethane. Organic layer is then separated and washed with water, dried over drying agents such as sodium sulfate and then concentrated. The residue obtained is purified by chromatography preferably over silica gel using eluant such as mixture of ethylacetate and chloroform to obtain compound of the formula 1b.

Compound of the formula Ic is obtained from compound of the formula Ia by treatment with oxidising agents preferably such as aqueous silver nitrate solution in the presence of an aqueous alkaline solution such as sodium hydroxide or potassium hydroxide and an organic water miscible solvent such as ethanol, methanol preferably being ethanol at temperatures from 0°C to 45°C, preferred being 27-30°C for a period from one hour to six hours, preferably for two hours. The reaction mixture is then filtered, concentrated and the residue is extracted with organic solvents such as ethylacetate or halogenated hydrocarbons such as chloroform, methylenechloride. Extracts after washing with water are dried over drying agents such as sodium sulfate and then concentrated. Residue obtained is purified either by crystallisation or by chromatography to obtain compounds of the formula Ic.

Compounds of the formula Id, wherein R₂ has the same meaning as defined earlier except 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α , 9,10,12 β ,12 α -dodecahydro-3 β ,6 α ,9 β -trimethylpyrano[4,3-j][1,2]-benzodioxepin-10-yl are prepared from compound of formula 1b by alkylation, preferably in the presence of a base such as sodium hydride in an anhydrous organic solvent such as benzene, toluene or dimethyl formamide, preferably dimethylformamide and halide of the formula R₂X', wherein R₂ has the same meaning as defined above and X' stands for halogen such as chloro or bromo at temperatures initially ranging from 0°C to 30°C, preferably at 0-5°C for a period from 5 minutes to 60 minutes preferably for 10-15 minutes and then at temperature 27°C for a period of one to six hours preferably for two hours. Reaction mixture after dilution with water is extracted with organic solvents such as petroleum ether, chloroform, ethylacetate and extracts after treatment with water and drying agents are concentrated and purified by column chromatography but in the case of compounds wherein R₂ has a basic group, reaction mixture is purified from organic solvent extract by acid base treatment to obtain compounds of the formula Id.

Compounds of the formula Id wherein R₂ stands for 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-3 β ,6 α ,9 β -trimethylpyrano[4,3-j][1,2]benzodioxepin-10-yl are also prepared from compound of the formula 1b by treatment with dihydroartemisinin, preferably in the presence of a catalyst such as borontrifluoride etherate at 0°C using organic solvent such as anhydrous methylene chloride for a period of fifteen minutes to one hour. The product is isolated from the reaction mixture by washing the reaction mixture with water, drying the organic layer, filtering and concentrating the filtrate under vacuum. Final purification is done by flash column chromatography using silica gel column to obtain α and β isomers.

Compounds of the formula 1e are prepared from compound 1b by treatment with a mixture of acid chlorides of the formula R₃COCl, wherein R₃ has the same meaning as defined above, preferably in the presence of an organic base such as N,N-dimethylaminopyridine, triethylamine or pyridine preferred being N,N-dimethylaminopyridine in organic solvent such as chloroform or dichloromethane at temperatures ranging from 0 to 35°C, preferably at 27-30°C for a period of one hour to six hours preferably for three hours. The reaction mixture is then diluted with water, extracted with organic solvent such as petroleum ether and petroleum ether extract is then washed with dilute hydrochloric acid followed by water and dried over anhydrous sodium sulphate and then concentrated. Residue is purified by chromatography to obtain compounds of the formula 1e.

Compounds of the formula 1f are prepared from compound of formula 1b by treatment with compound of formula R₄SO₂Cl preferably in pyridine wherein R₄ has the same meaning as defined earlier at temperatures ranging from 50 to 120°C, preferably at 90-100°C for a period of one to six hours, preferably for three hours. The reaction mixture after cooling to room temperature is diluted with water followed by extraction with organic solvents such as ethylacetate.

The ethylacetate extract is washed with dilute acetic acid, water, aqueous sodium bicarbonate and water in sequence and dried over anhydrous sodium sulfate and then concentrated after filtration to get residue which is purified by chromatography over silica gel to get compounds of formula 1f.

Compounds of the formula 1g are prepared from compound 1b by treatment with compounds of formula R₅NCX in an organic base such as triethylamine, diethylamine, benzylamine, N,N'-dimethylpyridine or

pyridine, preferably in pyridine wherein X stands for O or S and R_5 has the same meaning as defined above, at temperatures ranging from 30 to 80°C, preferably at 60°C for four hours to sixteen hours, preferably for fourteen hours. The reaction mixture preferably is then cooled to room temperature and diluted with water and extracted with organic solvent such as petroleum ether, ethyl acetate or chloroform.

- 5 The organic layer is then separated washed with dilute ice cold hydrochloric acid followed by water, dried over anhydrous sodium sulfate and concentrated under vacuum to obtain residue which is purified preferably by chromatography over silica gel to obtain compounds of the formula Ig.

- Compounds of the formula Ih, wherein R_6 , R_7 have the same meaning as defined earlier are preferably obtained from compound Ic by treatment first with thionylchloride in organic solvent such as ethylacetate at
10 temperatures ranging from 0 to 30°C, preferably at 10-19°C for a period of half an hour and subsequent treatment of the mixture with an amine of the formula NR_6R_7 wherein R_6 and R_7 have the same meaning as defined earlier. The temperature of the reaction mixture may be raised to 60-70°C and maintained for half an hour. The reaction mixture is then cooled to room temperature, diluted with water and extracted with organic solvents such as petroleum ether. The organic extract is washed with water, dried over sodium
15 sulfate and concentrated to obtain a residue which is repeatedly extracted with hot pentane to obtain compounds of the formula Ih.

- Compounds of the formula li wherein R_1 has the same meaning as defined earlier are preferably prepared from compound Ic by treatment with thionyl chloride in dry ethyl acetate at room temperature for half an hour followed by treating the mixture with pyridine in ethylacetate at temperatures 0-5°C for fifteen
20 minutes and then with alcohols of the formula R_1OH wherein R_1 has the same meaning as defined above maintaining the temperature at 0 to 5°C for further one hour. The reaction mixture is then extracted with organic solvent such as methylene chloride and the extract is washed with water, dilute hydrochloric acid and water and then concentrated after drying over drying agents such as sodium sulfate. Residue obtained is purified by flash chromatography using adsorbent such as silica gel and eluant such as chloroform, ethyl
25 acetate to get compounds of the formula li.

- Compound of the formula lj wherein R_8 and R_9 stand for carbethoxy is preferably prepared from compound Ia by treatment with a mixture of compounds of formula $CH_2R_8R_9$ wherein R_8 and R_9 are as defined above, pyridine and piperidine and heating the resulting mixture at 60 to 100°C preferably at 80°C for a period of 10 to 24 hours preferably 16 hours. The reaction mixture on cooling is treated with dilute
30 hydrochloric acid, extracted with petroleum ether and organic extract after washing with water, drying over sodium sulfate is concentrated and the residue obtained is purified by flash chromatography over silica gel to get compound of the formula lj.

- Compound of the formula lj wherein R_8 stands for hydrogen and R_9 stands for the meaning described above are preferably prepared from compound Ia by treatment with phosphoniumylides of formula
35 $Ph_3P=CHR_9$ wherein R_9 has the same meaning as above, at room temperature for two hours. The product is isolated by dilution with water, followed by extraction with chloroform. Chloroform extract is concentrated and residue obtained, purified by flash chromatography over silica gel using chloroform as eluant to obtain desired compound of the formula lj.

- The compounds of the instant invention may be of great use in the chemotherapy of human malaria and
40 viral infections. They have shown moderate to excellent antimalarial activity against both chloroquine sensitive and resistant strains of rodent malaria.

- The compounds of formula I may be administered in different manners, preferably perorally or parenterally in doses ranging from 2.5 to 100 mg/kg of body weight. As antimalarial drugs dosage unit forms such as dragees or capsules for oral administration or solutions and suspensions respectively for
45 injections, each containing 100 to 400 mg of active substance are preferred. Such dosage units are administered once to three times daily depending upon the condition of the patient.

- For oral administration, there may be used in particular tablets, dragees, capsules, powders or granules which contain the active substance together with the usual carriers, adjuvants and/or excipients such as starch, cellulose powder, talcum, magnesium stearate, sugar, gelatin, calcium carbonate, finely divided
50 silicic acid, carboxymethyl cellulose or similar substances.

- For parenteral administration, in particular for intramuscular injections, there may be used sterile suspensions for example oily suspensions prepared with the use of sesame oil, vegetable oil, castor oil or synthetic triglycerides, optionally with simultaneous use of surface active substances such as sorbitan fatty acid esters. Furthermore, there may also be used aqueous suspensions prepared for example with the use
55 of ethoxylated sorbitan fatty acid esters, optionally with addition of thickeners such as polyethylene glycol or carboxymethyl cellulose.

A. For Antimalarial Activity

The evaluation of blood-schizontocidal activity "28-day test" described by Raether and Fink [W.H.O. Report on the Scientific Working Group on the Chemotherapy in Malaria, TDR/Chemal 3rd Review, 85.3, Geneva, 3-5 June 1985 and references contained therein] was followed.

Mice: All experiments were carried out in random bred male and female Swiss mice obtained from the Hoechst India Limited breeding house at Mulund, Bombay. The animals were free from *Eperythrozoon coccoides*. The animals received food pellets and water ad lib and were kept at 22-25°C room temperature.

Parasite : *Plasmodium berghei* K-173 strain drug-sensitive and *berghei* (NS) moderately resistant to chloroquine were obtained from the London School of Hygiene and Tropical Medicines. The strains produce lethal infection at 1×10^7 parasitized red blood cells per mouse when inoculated either intraperitoneally or intravenously, between 6 to 7 days post infection.

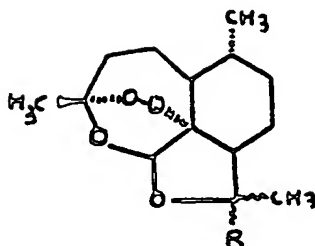
Administration of compounds: The compounds were administered orally or subcutaneously as per methods described by Raether and Fink [W.H.O. Report of the Scientific Working Group on the Chemotherapy in Malaria, TDR/Chemal 3rd Review, 85.3, Geneva, 3-5 June 1985 and references contained therein].

Compounds of the invention were homogenized in double refined Kardi oil or peanut oil or corn oil with one or two drops of polyoxyethylenesorbitan monooleate ([®]Tween-80, Sigma Chaniaallo, England) and such suspensions were used for subcutaneous inoculation in mice. Drugs were administered for 5 days. 1st dosing was done within 2 hours of infection (D + 0) followed by D + 1, D + 2, D + 3 and D + 4.

Observation of the treated mice: The blood smears were prepared at different intervals from D + 4 and continued up to D + 28. Blood smears were drawn from the terminal end of the tail and stained in Giemsa. Mice which were free from *berghei* on D + 28 were considered as completely cured.

Results obtained with the compounds of Formula I of the invention are listed in Table 2.

Table 2



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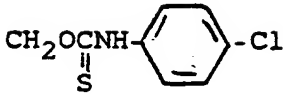
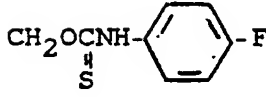
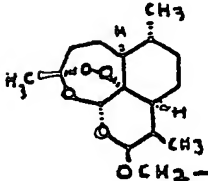
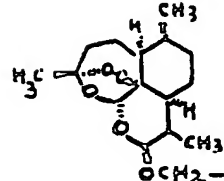
| R | Dose mg/kg x 5 | Route | Activity | |
|---|----------------------|-------|--|--|
| | | | No. of animals cured/ treated | No. of animals cured/ treated |
| | | | D + 7 | D + 28 |
| CHO | 25 | s.c. | 4/4 | 4/4 |
| CH ₂ OCH ₂ C≡CH | 10 | s.c. | 6/6 | 2/6 |
| CH ₂ OCH ₂ CH=CH ₂ | 5 | s.c. | 6/6 | 6/6 |
| CH ₂ OSO ₂ -  -CH ₃ | 5 | s.c. | 5/6 | 1/6 |

Table 2 (cont.)

| R | Dose mg/kg x 5 | Route | Activity | |
|---|----------------------|-------|-------------------|-------------------|
| | | | No. of | No. of |
| | | | animals | animals |
| | | | cured/ treated | cured/ treated |
| | | | D + 7 | D + 28 |
| <hr/> | | | | |
|  | 5 | s.c. | 12/12 | 12/12 |
| | 2.5 | s.c. | 6/6 | 3/6 |
| | 25 | p.o. | 6/6 | 6/6 |
| | 5 | s.c. | 5/5 | 6/6 ^{*)} |
| | 2.5 | s.c. | 5/5 | 2/5 ^{*)} |
| | 25 | p.o. | 5/5 | 5/5 ^{*)} |
|  | 5 | s.c. | 6/6 | 6/6 |
| | | | | |
|  | 2.5 | s.c. | 12/12 | 12/12 |
| | 1.25 | s.c. | 11/11 | 9/11 |
| | 25 | p.o. | 6/6 | 5/6 |
| | 5.0 | s.c. | 8/8 | 8/8 ^{*)} |
| | 2.5 | s.c. | 8/8 | 7/8 ^{*)} |
|  | 5 | s.c. | 5/5 | 5/5 |
| | 2.5 | s.c. | 5/5 | 5/5 |
| | 25 | p.o. | 6/6 | |
| | 5 | s.c. | 6/6 ^{*)} | |
| | 2.5 | s.c. | 6/6 ^{*)} | |

Activity reported for all compounds is against chloroquine sensitive strain (P. berahei X-173). Activity reported with * is against chloroquine resistant strain.

B. For Antiviral Activity

Infection is given to Swiss mice (25 g body weight) either by intravenous or by intraperitoneal route with Friend's leukemia virus collected from serum of the previously infected mice diluted (1:50) with sterile
 5 Dulbecco's buffer saline.

The compounds were administered either by subcutaneous or intramuscular or oral or intraperitoneal route. The treatment started two days prior to the infection and continued for 8 more days post infection. Autopsy was done 2 days after the drug administration was over.

The compounds were tested against Friend's leukemia virus infection in mice and showed activity at a
 10 dose of 1 to 5 mg/mouse/day for 10 days. The reduction of the spleen weight as compared with the infected untreated control was considered as activity. The results indicate that such compounds may be active against Human Immunodeficiency Virus (HIV) infection in man.

The following examples illustrate the invention but do not limit the scope of the invention.

15 Example 1

3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a α ,9,10,12 β ,12a-dodecahydro-9-bromo-10-hydroxy-3 β ,6 α ,9-trimethylpyrano-[4,3-j][1,2]benzodioxepin

20 To the solution of 3 α ,12 α -Epoxy-3,4,5,5a α ,6,7,8,8a α ,12 β ,12a-decahydro-3 β ,6 α ,9-trimethylpyrano[4,3-j]-[1,2]benzo dioxepin-9-ene (1.0 g) in carbon tetrachloride (100 ml), water (0.5 ml) was added. To this stirred solution liquid bromine was added dropwise with a capillary tube until a pale bromine colour was persistent. The reaction mixture was stirred for further 1 hr. The reaction mixture was diluted with carbontetrachloride (100 ml), washed with water, dried (Na₂SO₄) and solvent removed under vacuum. The solid obtained was
 25 purified by flash chromatography over silica gel. Elution with ethyl acetate/chloroform gave the product after concentration of eluants, m.p. 124-125° C (d) Yield 79%.

Example 2

30 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-carboxaldehyde

To the solution of 3 α ,11 α -epoxy-3,4,5,5a α ,6,7,8,8a α ,9,10,12 β ,12a-dodecahydro-9-bromo-10-hydroxy-3 β ,6 α ,9-trimethylpyrano-[4,3-j][1,2]benzodioxepin (0.19 g) in chloroform (5 ml), diazabicycloundecene (DBU,
 35 0.2 ml) was added at room temperature. The reaction mixture was stirred for 45 minutes, solvent was then removed under vacuum and the residue was purified by chromatography over silica gel using chloroform as an eluant to give 0.13 g of the title product in first few fractions; m.p. 100° C, yield 85%.

Example 3

40 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a α ,9,11,11a-undecahydro-9-hydroxymethyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin

To the solution of 3 α ,11 α -epoxy-3,4,5,5a α ,6,7,8,8a α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j]-
 45 [1,2]benzodioxepin-9-carboxaldehyde (1.0 g) in ethanol (60 ml), sodium borohydride (0.1 g) was added. The reaction mixture was stirred for 30 mins. Aqueous ammonium chloride was then added to decompose the excess of NaBH₄. Ethanol was removed under vacuum and the product was extracted with dichloromethane (3 X 25 ml). Combined dichloromethane extract was washed with water, aqueous sodium chloride, dried (Na₂SO₄) and solvent removed. The product was purified by flash chromatography over silica gel using 8%
 50 ethyl acetate in chloroform as an eluant to get the product, m.p. 135-136° C; yield 72%.

Example 4

55 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-carboxylic acid

To the stirred solution of 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a α , 9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxaldehyde (0.9 g) in ethanol (5 ml) a solution of silver

nitrate (1.8 g) in water (3.0 ml) was added. To this stirred reaction mixture a solution of sodium hydroxide (0.4 g) in water (2.0 ml) was added dropwise. The reaction mixture was stirred for further 2 hours at room temperature. The residue was then filtered and washed with 5.0 ml of aqueous alcohol. Alcohol was removed from the combined filtrate, under vacuum. The aqueous layer was diluted with water and extracted with chloroform (2 X 10 ml). The aqueous layer was then acidified with acetic acid. Extraction of the acidified layer followed by concentration of extract and crystallisation from isopropyl ether - petroleum ether gave the title product; 0.72 g (75.79%) m.p. 166-167° C.

Example 5

10

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-9-(2-propynyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j]-[1,2]-benzodioxepin

To the stirred, ice cold, suspension of NaH (20 mg) in DMF (0.5 ml), propargyl bromide (0.1 ml) and 3 α ,11 α -Epoxy-3,4,5, 5 α ,6,7,8,8a,9,11,11a-undecahydro-9-hydroxymethyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin (60 mg) were added. The reaction mixture was slowly brought to room temperature and stirred for 2 hr. Water was then added to the reaction mixture and the product was extracted in petroleum ether (60-80° C). The product was purified by flash chromatography over silica gel; m.p. 105° C, yield 71%. Similarly following compounds were prepared, using appropriate halide in place of propargyl bromide.

20 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-9-(N,N-diethylaminoethoxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin, an oil, yield 47 %.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-9-(2-propenyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin, an oil, yield 45 %.

25 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-9-(3-phenyl-2-propenyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin, an oil, yield 42 %.

Example 6

30 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-9-(chloroacetoxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin

To the stirred solution of dimethylaminopyridine (DMAP) (0.1 g) in chloroform at room temperature chloroacetylchloride (0.1 ml) was added. The resulting mixture was stirred for 20 mins and then 3 α ,11 α -epoxy-3,4,5, 5 α ,6,7,8,8a,11,11a-undecahydro-9-hydroxymethyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin (0.07 g) was added. The reaction mixture was stirred for further 3 hrs. Water was added to the reaction mixture and the product was extracted in petroleum ether. The petroleum ether extract was washed with dil. HCl, water, dried (Na₂SO₄) and solvent removed. The product when purified by flash chromatography over silica gel was obtained, as an oil, yield 42%.

40 Similarly following compounds were prepared using appropriate acid chloride in place of chloroacetylchloride.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-(4-chlorobutyryloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin, an oil, yield 35 %.

Example 7

45

Preparation of 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-9-methylsulfonyloxymethyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin

50 A mixture of 3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-hydroxymethyl-3 β ,6 α ,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin (0.06 g) and methanesulfonylchloride (0.1 ml) in pyridine (0.3 ml) was heated at 90-100° C for 3 hrs. The reaction mixture was then cooled, diluted with water and the product was extracted with ethyl acetate. The ethyl acetate extract was washed with diluted acetic acid, water, aqueous sodium bicarbonate, water, dried (Na₂SO₄) and solvent removed to get an oil. The product was purified by flash chromatography over silica gel.

55 Similarly following sulfonate esters were prepared using appropriate sulfonyl chlorides in place of methylsulfonylchloride.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-(p-toluenesulfonyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin, an oil, yield 33 %.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-(phenylsulfonyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin, an oil, yield 27 %.

Example 8

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-(4-chlorophenylaminothiocarbonyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin

A mixture of 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-hydroxymethyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin (0.1 g) and 4-chlorophenylisothiocyanate (0.15 g) in pyridine was heated at 60 °C for 14 hrs. The reaction mixture was then cooled, diluted with water and extracted with petroleum ether (60-80 °C). The combined extract was washed with diluted ice cold HCl, water, dried (Na₂SO₄) and solvent removed. The product was purified by flash chromatography over silica gel, m.p. 89-90 °C, yield 65 %.

Similarly the following compounds were prepared using appropriate isocyanate or isothiocyanate in place of 4-chlorophenylisothiocyanate.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-(4-chlorophenylaminocarbonyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin, mp. 160 °C, yield 42 %.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-(4-fluorophenylaminothiocarbonyloxymethyl)-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin, mp. 79-80 °C, yield 37 %.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-(2-propenylaminothiocarbonyloxymethyl)-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin, an oil, yield 23 %.

Example 9

Preparation of 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-9-(4-trifluoromethylphenylmethylaminocarboxamido)-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin

To the stirred solution of 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-carboxylic acid (0.07 g) in dry ethyl acetate (2.5 ml), thionyl chloride (0.1 ml) was added dropwise. The reaction mixture was stirred for half an hour and then solution of 4-trifluoromethylbenzylamine (0.2 ml) in dry ethyl acetate (2 ml) was added with cooling in ice-water bath. The reaction mixture was stirred for further half an hour at 60-70 °C, water was added, product was extracted with petroleum ether (60-80). Combined extract was washed repeatedly with water, dried and solvent removed. The residue obtained was repeatedly extracted with hot n-pentane to get the product amide, mp. 170-172 °C, yield 25%.

Similarly the following amides were prepared using appropriate amines in place of 4-trifluoromethylbenzylamine.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-9-(N-morpholinoyl)-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin, an oil, yield 43 %.

3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-9-(N-methylpiperazinoyl)-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin, mp. 93 °C, yield 43 %.

Example 10

Preparation of 2-Chloroethyl 3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8a, 9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-carboxylate

To the stirred solution of 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8a, 9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-carboxylic acid (0.05 g) in dry ethyl acetate (2 ml), thionylchloride (0.1 ml) was added dropwise. The reaction mixture was stirred for half an hour and then solution of pyridine (0.2 ml) in dry ethyl acetate was added, with cooling. The reaction mixture was stirred for 15 minutes and then 2-chloroethanol (0.2 ml) was added. The reaction mixture was stirred for further 1 hr, water was added and the product extracted with dichloromethane. The extract was washed with water, cold diluted HCl, water, dried (Na₂SO₄) and solvent removed. The product was purified by flash chromatography over silica gel, mp. 112 °C, yield 46%.

Similarly the following esters were prepared using appropriate alcohol in place of 2-chloroethanol.

2-Propenyl 3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8a,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-

benzodioxepin-9-carboxylate, an oil, yield 38 %.

2-Bromoethyl 3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxylate, an oil, yield 47 %.

3-Chloropropyl 3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin-9-carboxylate, an oil, yield 24 %.

Ethyl 3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxylate, an oil, yield 29 %.

8-Chlorooctyl 3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxylate, an oil, yield 21 %.

Example 11

Preparation of 1-(3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-yl)-2,2'-dicarboethoxyethylene

A mixture of 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin-9-carboxaldehyde (0.08 g) diethyl malonate (0.3 ml), pyridine (0.3 ml) and piperidine (1.0 ml) was heated with stirring at 80 °C for 16 hrs. The reaction mixture was cooled, treated with diluted HCl and was then extracted with petroleum ether (60-80). The extract was washed with water, dried (Na₂SO₄) and solvent removed. The residue was flash chromatographed over silica gel to get the title compound, as an oil, yield 22%.

Example 12

Preparation of 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-9-(cis-4-trifluoromethylstyryl)-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin

To the stirred solution of the triphenyl p-trifluoromethylbenzyl phosphonium bromide (0.18 g) in dry tetrahydrofuran (2 ml), sodium hydride (0.03 g) was added. The reaction mixture was stirred for 30 mins at room temperature: 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j]-[1,2]benzodioxepin-9-carboxaldehyde (5) (0.09 g) was then added to the above phosphonium ylide and the reaction mixture stirred for further 2 hrs. Water was then added to the reaction mixture and product extracted with chloroform. Residue from concentration of chloroform extract was purified by flash chromatography over silica gel, using chloroform as an eluant, first gave trans product in 9% yield. Further elution gave cis product in 26% yield.

Similarly following the conditions described using triethyl phosphonoacetate in place of triphenyl p-trifluoromethylbenzyl phosphonium bromide, the compound cis-1-(3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-yl)-2-carboethoxyethylene was obtained as an oil, yield 54 %.

Example 13

Preparation of 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-10 α -[3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylene]oxy-3 β ,6 α ,9 β -trimethylpyrano[4,3-j]-[1,2]benzodioxepin

To a solution of dihydroartemisinin (0.490 g; 1.70 mmol) and 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-9-hydroxymethyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin (0.350 gm; 1.23 mmol) in dry methylenechloride (70.0 ml) borontrifluoride etherate (0.2 ml) was added dropwise at 0 °C. Reaction mixture was stirred for 15 minutes and then washed with water. The organic layer was separated, dried, filtered and filtrate was concentrated. Residue obtained after concentration, was purified by flash chromatography using silica gel column to obtain the product. mp. 100 °C, yield 21%.

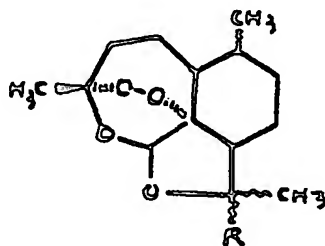
Example 14

Preparation of 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-10 β -[3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]oxy-3 β ,6 α ,9 β -trimethylpyrano[4,3-j][1,2]benzodioxepin

To a solution of dihydroartemisinin (0.490 gm; 1.70 mmol) and 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-hydromethyl-3 β ,6 α ,9-trimethylfurano[3,4-*j*][1,2]benzodioxepin (0.350 gm; 1.23 mmol) in dry methylenechloride (70.0 ml), borontrifluoride-etherate (0.2 ml) was added drop wise at 0°C. Reaction was stirred for 15 minutes and then washed with water. The organic layer was separated, dried, filtered and filtrate was concentrated. Residue obtained after concentration, was purified by flash chromatography using silica gel column. The first few fractions of α -isomer were discarded. Further elution gave the fractions containing the title compound pure product, mp 154-156°C, yield 34%.

Claims

1. Compound of formula I



wherein R stands for
CHO;

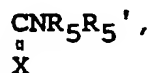
COOR₁,

wherein R₁ stands for hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl group;

CH₂OR₂,

wherein R₂ stands for hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, dialkylamino alkyl group or 3 α ,12 α -Epoxy-3,4,5, 5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-3 β ,6 α ,9 β -trimethylpyrano[4,3-*j*][1,2]benzodioxepin-10-yl or a group COR₃,

wherein R₃ stands for alkyl, substituted alkyl group, or a group SO₂R₄, wherein R₄ stands for alkyl or aryl group, or a group



wherein X denotes O or S,

R₅ stands for hydrogen,

R₅' stands for alkyl or aryl group or

NR₅R₅', stands for heterocycle;

CONR₆R₇,

wherein R₆ stands for hydrogen, aralkyl, R₇ stands for hydrogen, alkyl, aryl, aralkyl group or R₆ and R₇ together with the nitrogen to which they are attached form a heterocycle which may contain an additional hetero atom and is optionally substituted at one or more places;

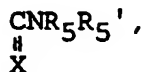
CH = CR₈R₉,

wherein R₈ stands for hydrogen, carboxyalkyl and R₉ stands for carboxyalkyl, aryl or heterocycle;

COSR₁₀,

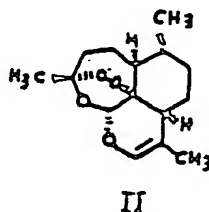
wherein R₁₀ stands for alkyl, substituted alkyl or aryl groups;
and pharmaceutically acceptable salts thereof.

2. Compounds of formula I as claimed in claim 1, wherein R stands for CHO or CH₂OR₂, R₂ denoting hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, dialkylamino alkyl group or 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-3 β ,6 α ,9 β -trimethylpyrano[4,3-*j*][1,2]benzodioxepin-10-yl or a group COR₃, wherein R₃ stands for alkyl, substituted alkyl group, or a group SO₂R₄, wherein R₄ stands for alkyl or aryl group, or a group

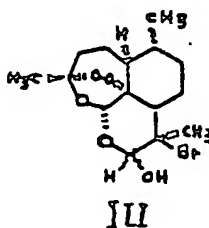


5 wherein X denotes O or S.

3. Compounds as claimed in claims 1 or 2 which are
- 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-formyl-3 β ,6 α ,9-trimethylfurano[3,4-*j*][1,2]-benzodioxepin,
- 10 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(2-propynyloxy)methyl-3 β ,6 α ,9-trimethylfurano-[3,4-*j*][1,2]-benzodioxepin,
- 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(2-propenoxy)methyl-3 β ,6 α ,9-trimethylfurano-[3,4-*j*][1,2]-benzodioxepin,
- 15 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(*p*-toluenesulfonyloxy)methyl-3 β ,6 α ,9-trimethylfurano-[3,4-*j*][1,2]benzodioxepin,
- 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(4-chlorophenylaminothiocarbonyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-*j*][1,2]benzodioxepin,
- 3 α ,11 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-9-(4-fluorophenylaminothiocarbonyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-*j*][1,2]benzodioxepin,
- 20 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-10 α -[3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,11,11 α -undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-*j*][1,2]benzodioxepin-9-methylen]-oxy-3 β ,6 α ,9 β -trimethylpyrano-[4,3-*j*][1,2]benzodioxepin und
- 3 α ,12 α -Epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,12 β ,12 α -dodecahydro-10 β -[3 α ,11 α -epoxy-3,4,5,5 α ,6,7,8,8 α ,9,10,11,11 α -undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-*j*][1,2]benzodioxepin-9-methylen]oxy-3 β ,6 α ,9 β -trimethylpyrano-[4,3-*j*][1,2]benzodioxepin.
- 25
4. A process for the production of compounds of the formula I according to one or more of the preceding claims, wherein a compound of formula II

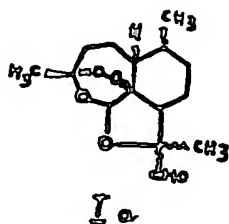


40 is treated with a brominating agent and subsequently hydrolyzed to a compound of formula III



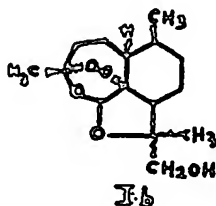
55 which is for the preparation of compounds of formula Ia

5



10 treated with an organic base, or wherein, for the preparation of compounds of formula Ib,

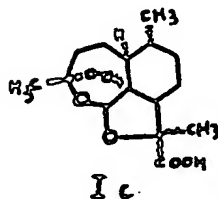
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compounds of formula Ia are treated with a reducing agent, or wherein for the preparation of compounds of formula Ic

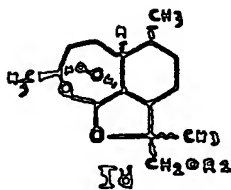
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compounds of formula Ia are treated with an oxidizing agent or wherein for the preparation of compounds of formula Id

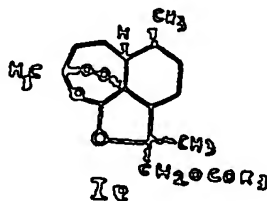
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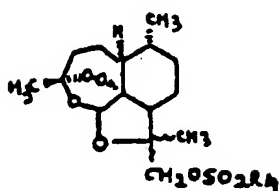
compounds of formula Ib are alkylated or are reacted with dihydroartemisinin, or wherein for the preparation of compounds of formula Ie

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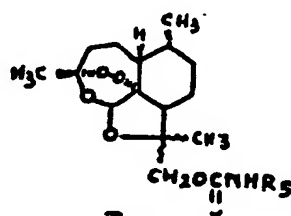
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55 compounds of formula Ib are treated with acid chlorides of the formula R_3COCl , or wherein for the preparation of compounds of formula If



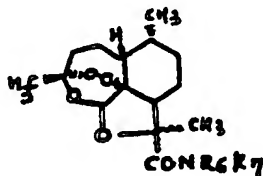
I f

compounds of formula Ib are reacted with compounds of the formula R_4SO_2Cl or wherein for the preparation of compounds of formula Ig



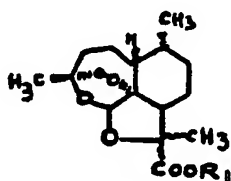
I g

compounds of formula Ib are reacted with compounds of the formula R_5NCX , or wherein for the preparation of compounds of formula Ih



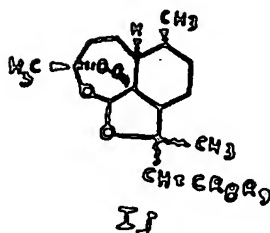
I h

compounds of formula Ic are reacted with thionylchloride and subsequently with compounds of the formula NR_6R_7 , or wherein for the preparation of compounds of the formula li



I i

compounds of formula Ic are reacted with thionylchloride and subsequently with a compound of the formula R_1OH or wherein for the preparation of compounds of the formula lj



wherein R_8 and R_9 stand for carboethoxy a compound of the formula Ia is treated with compounds of the formula $CH_2R_8R_9$

or wherein for the preparation of compounds of the formula Ij, wherein R_8 stands for hydrogen and R_9 stands for carboalkyl, aryl or a heterocycle,

a compound of the formula Ia is treated with compounds of the formula $Ph_3P=CHR_9$,

the substituents $R_1 - R_9$ having - where not especially defined - the same meanings as in the preceding claims.

5. A pharmaceutical which contains at least one of the compounds as claimed in one or more of claims 1 - 3.

6. A process for the production of a pharmaceutical as claimed in claim 5, wherein a compound of formula I is transformed into a form suitable for administration.

7. The use of compounds of formula I as claimed in one or more of claims 1 - 3 for the prophylaxis or the treatment of malaria.

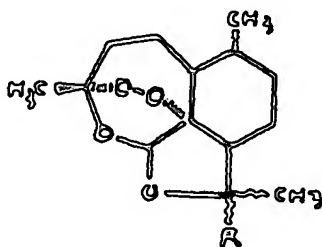
8. The use of compounds of formula I as claimed in one or more of claims 1 - 3 for the prophylaxis or the treatment of diseases caused by viruses.

9. A method of treatment for malaria, wherein a pharmaceutical as claimed in claim 5 is administered.

10. A method of treatment for virus diseases wherein a pharmaceutical as claimed in claim 5 is administered.

Claims for the following Contracting States: ES, GR

1. A process for the production of compounds of the formula I,



wherein R stands for

CHO;

$COOR_1$,

wherein R_1 stands for hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl group;

CH_2OR_2 ,

wherein R_2 stands for hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, dialkylamino alkyl group or $3\alpha,12\alpha$ -Epoxy-3,4,5, $5\alpha,6,7,8,8\alpha,9,10,12\beta,12\alpha$ -dodecahydro-3 $\beta,6\alpha,9\beta$ -trimethylpyrano[4,3-j][1,2]benzodioxepin-10-yl or a group $CO R_3$.

wherein R_3 stands for alkyl, substituted alkyl group, or a group SO_2R_4 , wherein R_4 stands for alkyl or aryl group, or a group

5



wherein X denotes O or S,

R_5 stands for hydrogen,

10 R_5' stands for alkyl or aryl group or

NR_5R_5' , stands for heterocycle;

$CONR_5R_7$,

wherein R_5 stands for hydrogen, aralkyl, R_7 stands for hydrogen, alkyl, aryl, aralkyl group or R_5 and R_7 together with the nitrogen to which they are attached form a heterocycle which may contain an

15

$CH = CR_8R_9$,

wherein R_8 stands for hydrogen, carboxyalkyl and R_9 stands for carboxyalkyl, aryl or heterocycle;

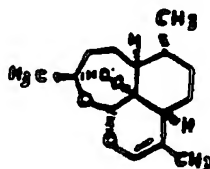
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CO_2R_{10} ,

wherein R_{10} stands for alkyl, substituted alkyl or aryl groups;

and pharmaceutically acceptable salts thereof, wherein a compound of formula II

25

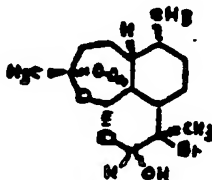


II

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is treated with a brominating agent and subsequently hydrolyzed to a compound of formula III

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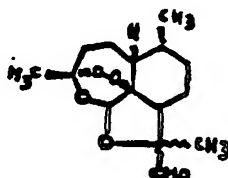


III

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which is for the preparation of compounds of formula Ia

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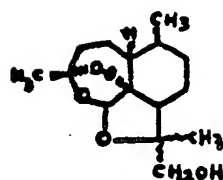


Ia

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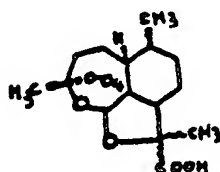
treated with an organic base, or wherein, for the preparation of compounds of formula Ib,

55



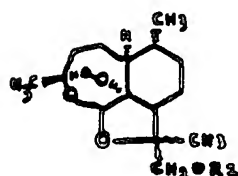
Ib

compounds of formula Ia are treated with a reducing agent, or wherein for the preparation of compounds of formula Ic



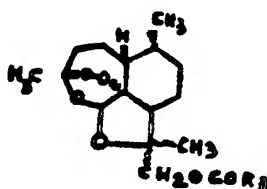
Ic

compounds of formula Ia are treated with an oxidizing agent or wherein for the preparation of compounds of formula Id



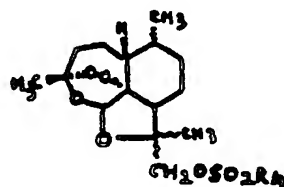
Id

compounds of formula Ib are alkylated or are reacted with dihydroartemisinin, or wherein for the preparation of compounds of formula Ie



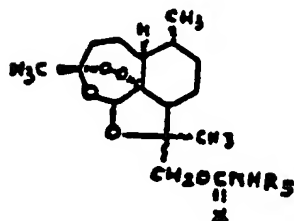
Ie

compounds of formula Ib are treated with acid chlorides of the formula $R_3\text{COCl}$, or wherein for the preparation of compounds of formula If



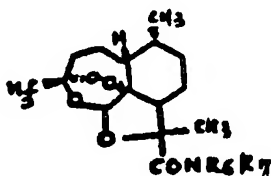
If

compounds of formula Ib are reacted with compounds of the formula $R_4\text{SO}_2\text{Cl}$ or wherein for the preparation of compounds of formula Ig



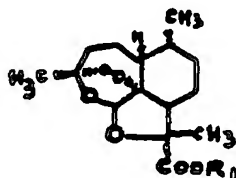
Ig

10 compounds of formula Ib are reacted with compounds of the formula R_5NCX ,
or wherein for the preparation of compounds of formula Ih



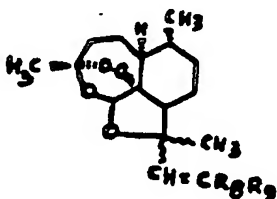
Ih

15 compounds of formula Ic are reacted with thionylchloride and subsequently with compounds of the
formula NR_6R_7 ,
or wherein for the preparation of compounds of the formula li



Ii

20 compounds of formula Ic are reacted with thionylchloride and subsequently with a compound of the
formula R_1OH
or wherein for the preparation of compounds of the formula lj

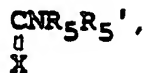


Ij

25 wherein R_8 and R_9 stand for carbethoxy a compound of the formula Ia is treated with compounds of the
formula $CH_2R_8R_9$
or wherein for the preparation of compounds of the formula lj, wherein R_8 stands for hydrogen and R_9
stands for carboalkyl, aryl or a heterocycle,
a compound of the formula Ia is treated with compounds of the formula $Ph_3P=CHR_9$,
the substituents $R_1 - R_9$ having - where not especially defined - the same meanings as defined in
connection with formula I.

- 30 2. A process for the production of compounds of formula I as claimed in claim 1, wherein R stands for
CHO or CH_2OR_2 , R_2 denoting hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl,
substituted alkynyl, dialkylamino alkyl group or $3\alpha,12\alpha$ -Epoxy-3,4,5,5a,6,7,8,8a,9,10,12,12a-
dodecahydro-3,6,9-trimethylpyrano[4,3-j][1,2]benzodioxepin-10-yl or a group COR_3 , wherein R_3

stands for alkyl, substituted alkyl group, or a group SO_2R_4 , wherein R_4 stands for alkyl or aryl group, or a group



wherein X denotes O or S.

3. A process for the production of compounds as claimed in claims 1 or 2 which are
 - 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a,9,11,11a-undecahydro-9-formyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]-benzodioxepin,
 - 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a,9,11,11a-undecahydro-9-(2-propynoxy)methyl-3 β ,6 α ,9-trimethylfurano-[3,4-j][1,2]-benzodioxepin,
 - 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a,9,11,11a-undecahydro-9-(2-propenoxy)methyl-3 β ,6 α ,9-trimethylfurano-[3,4-j][1,2]-benzodioxepin,
 - 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a,9,11,11a-undecahydro-9-(p-toluenesulfonyloxy)methyl-3 β ,6 α ,9-trimethylfurano-[3,4-j][1,2]benzodioxepin,
 - 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a,9,11,11a-undecahydro-9-(4-chlorophenylaminothiocarbonyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin,
 - 3 α ,11 α -Epoxy-3,4,5,5a α ,6,7,8,8a,9,11,11a-undecahydro-9-(4-fluorophenylaminothiocarbonyloxy)methyl-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin,
 - 3 α ,12 α -Epoxy-3,4,5,5a α ,6,7,8,8a α ,9,10,12 β ,12a-dodecahydro-10 α -[3 α ,11 α -epoxy-3,4,5,5a α ,6,7,8,8a,9,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]-oxy-3 β ,6 α ,9 β -trimethylpyrano-[4,3-j][1,2]benzodioxepin und
 - 3 α ,12 α -Epoxy-3,4,5,5a α ,6,7,8,8a α ,9,10,12 β ,12a-dodecahydro-10 β -[3 α ,11 α -epoxy-3,4,5,5a α ,6,7,8,8a,9,10,11,11a-undecahydro-3 β ,6 α ,9-trimethylfurano[3,4-j][1,2]benzodioxepin-9-methylen]oxy-3 β ,6 α ,9 β -trimethylpyrano-[4,3-j][1,2]benzodioxepin.
4. A process for the production of a pharmaceutical which contains at least one of the compounds as claimed in one or more of claims 1 - 3, wherein a compound of formula I is transformed into a form suitable for administration.
5. The use of compounds of formula I as claimed in one or more of claims 1 - 3 for the prophylaxis or the treatment of malaria.
6. The use of compounds of formula I as claimed in one or more of claims 1 - 3 for the prophylaxis or the treatment of diseases caused by viruses.
7. A method of treatment for malaria, wherein a pharmaceutical as claimed in claim 4 is administered.
8. A method of treatment for virus diseases wherein a pharmaceutical as claimed in claim 4 is administered.



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PARTIAL EUROPEAN SEARCH REPORT
which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application number

EP 91 10 7304

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|---|---|--|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl. ⁴) |
| X | WO-A-88 04 660 (SRI INTERNATIONAL) * Claims 6,28 * -- | 1,7 | C 07 D 493/20 A 61 K 31/34/ (C 07 D 493/20 C 07 D 323:00 C 07 D 321:00 C 07 D 307:00) |
| A | EP-A-0 362 730 (HOECHST AG) * Claims 1,6-8 * ----- | 1,7,8 | |
| | | | TECHNICAL FIELDS SEARCHED (Int. Cl. ⁴) |
| | | | C 07 D 493/00 A 61 K 31/00 |
| INCOMPLETE SEARCH | | | |
| <p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 1-8 Claims searched incompletely: Claims not searched: 9,10 Reason for the limitation of the search:</p> <p>Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)</p> | | | |
| Place of search THE HAGUE | | Date of completion of the search 08-07-1991 | Examiner VOYIAZOGLOU |
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